

FORM PTO-1390 (REV. 11-2000)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER 830010-2006.2
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known see 37 C.F.R. 1.5) 09/806645
INTERNATIONAL APPLICATION NO. PCT/US99/16049	INTERNATIONAL FILING DATE 15 July 1999	PRIORITY DATE CLAIMED 16 July 1998
TITLE OF INVENTION TOPICAL COMPOSITIONS COMPRISING AN OPIOID ANALGESIC AND AN NMDA ANTAGONIST		
APPLICANT(S) FOR DO/EO/US Yuri KOLESNIKOV and Gavril W. PASTERNAK		
<p>Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:</p> <p>1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input type="checkbox"/> This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).</p> <p>4. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))</p> <p>a. <input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau).</p> <p>b. <input type="checkbox"/> has been communicated by the International Bureau.</p> <p>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</p> <p>6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).</p> <p>7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))</p> <p>a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau).</p> <p>b. <input type="checkbox"/> have been communicated by the International Bureau.</p> <p>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</p> <p>d. <input checked="" type="checkbox"/> have not been made and will not be made.</p> <p>8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p> <p>Items 11 to 20 below concern document(s) or information included:</p> <p>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input type="checkbox"/> A FIRST preliminary amendment.</p> <p>14. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.</p> <p>15. <input type="checkbox"/> A substitute specification.</p> <p>16. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.</p> <p>18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).</p> <p>19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</p> <p>20. <input checked="" type="checkbox"/> Other items or information:</p> <p>PCT/RO/101, PCT/ISA/220, 210, 6 sheets of drawings PCT/IPEA/419, 409, PCT/IPEA/402, 401, 408 Petition to Revive an Unintentionally Abandoned National Phase Application Under 37 C.F.R. 1.137(b), Check for \$1,240.00</p>		


EXPRESS MAILMailing Label Number: **EL585030083US**Date of Deposit: **April 2, 2001**

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Charles J. Jackson
(Typed or printed name of person mailing paper or fee)

Charles J. Jackson
(Signature of person mailing paper or fee)

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21. <input checked="" type="checkbox"/> The following fees are submitted		CALCULATIONS PTO USE ONLY																																				
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1000.00 International preliminary examination fee (37 C.F.R. 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00		<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">ENTER APPROPRIATE BASIC FEE AMOUNT =</td> <td style="width: 20%; text-align: right;">\$ 860.00</td> </tr> <tr> <td>Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).</td> <td style="text-align: right;">\$</td> </tr> <tr> <td> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">CLAIMS</td> <td style="width: 33%;">NUMBER FILED</td> <td style="width: 33%;">NUMBER EXTRA</td> <td style="width: 33%;">RATE</td> </tr> <tr> <td>Total Claims</td> <td><u>18</u> - 20 =</td> <td><u>0</u></td> <td>x \$18.00</td> </tr> <tr> <td>Independent Claims</td> <td><u>5</u> - 3 =</td> <td><u>2</u></td> <td>x \$80.00</td> </tr> </table> </td> <td style="text-align: right;">\$ 160.00</td> </tr> <tr> <td>MULTIPLE DEPENDENT CLAIM(S) (if applicable)</td> <td style="text-align: right;">+ \$270.00</td> </tr> <tr> <td>TOTAL OF ABOVE CALCULATIONS =</td> <td style="text-align: right;">\$1,020.00</td> </tr> <tr> <td><input type="checkbox"/> Applicant claims small entity status. See 37 C.F.R. 1.27. The fees indicated above are reduced by 1/2.</td> <td style="text-align: right;">\$</td> </tr> <tr> <td>SUBTOTAL =</td> <td style="text-align: right;">\$1,020.00</td> </tr> <tr> <td>Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).</td> <td style="text-align: right;">\$</td> </tr> <tr> <td>TOTAL NATIONAL FEE =</td> <td style="text-align: right;">\$1,020.00</td> </tr> <tr> <td>Fee for recording the enclosed assignments (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property</td> <td style="text-align: right;">\$</td> </tr> <tr> <td>TOTAL FEES ENCLOSED =</td> <td style="text-align: right;">\$1,020.00</td> </tr> <tr> <td> I do not receive the following amount(s) <u>Receive only \$260</u> </td> <td style="text-align: right;"> Amount to be refunded: \$ charged: \$ </td> </tr> </table>	ENTER APPROPRIATE BASIC FEE AMOUNT =	\$ 860.00	Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	\$	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">CLAIMS</td> <td style="width: 33%;">NUMBER FILED</td> <td style="width: 33%;">NUMBER EXTRA</td> <td style="width: 33%;">RATE</td> </tr> <tr> <td>Total Claims</td> <td><u>18</u> - 20 =</td> <td><u>0</u></td> <td>x \$18.00</td> </tr> <tr> <td>Independent Claims</td> <td><u>5</u> - 3 =</td> <td><u>2</u></td> <td>x \$80.00</td> </tr> </table>	CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	Total Claims	<u>18</u> - 20 =	<u>0</u>	x \$18.00	Independent Claims	<u>5</u> - 3 =	<u>2</u>	x \$80.00	\$ 160.00	MULTIPLE DEPENDENT CLAIM(S) (if applicable)	+ \$270.00	TOTAL OF ABOVE CALCULATIONS =	\$1,020.00	<input type="checkbox"/> Applicant claims small entity status. See 37 C.F.R. 1.27. The fees indicated above are reduced by 1/2.	\$	SUBTOTAL =	\$1,020.00	Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	\$	TOTAL NATIONAL FEE =	\$1,020.00	Fee for recording the enclosed assignments (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property	\$	TOTAL FEES ENCLOSED =	\$1,020.00	I do not receive the following amount(s) <u>Receive only \$260</u>	Amount to be refunded: \$ charged: \$
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a. <input checked="" type="checkbox"/> Two checks in the amount of \$4260.00 to cover the above fees are enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-0320 . A duplicate copy of this sheet is enclosed. d. <input type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.																																						
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.																																						
SEND ALL CORRESPONDENCE TO: Susan K. Lehnhardt, Esq. FROMMER LAWRENCE & HAUG LLP 745 Fifth Avenue New York, NY 10151																																						
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° TOPICAL COMPOSITIONS COMPRISING AN OPIOID ANALGESIC AND AN NMDA
ANTAGONIST

5 This application claims priority to provisional U.S. application Serial
No. 60/092,982 filed July 16, 1998 which is incorporated herein by reference in its
entirety.

10 This invention was made with government support under Grant
Number DA07242, DA00220 and CA08748 awarded by The National Institutes of
Health. The U.S. government has certain rights in the invention.

FIELD OF THE INVENTION

15 The invention is directed to topical pharmaceutical compositions of
an N-methyl-D-aspartate receptor antagonist alone or in combination with an
analgesic that functions through an opiate receptor for peripheral analgesia and uses
of the topical pharmaceutical compositions for treatment of pain, with no/or
minimal tolerance development to the analgesic.

BACKGROUND OF THE INVENTION

20 Morphine is a potent mu opioid receptor agonist with important
central sites of action (Reisine and Pasternak, 1996). Peripheral mechanisms also
have been reported and their importance is becoming increasingly appreciated (Stein
et al., 1995; Barber and Gottschlich, 1992; Joris *et al.*, 1987; Junien and Wettstein,
1992). Peripheral analgesics have a number of potential advantages in the clinical
25 treatment of pain, particularly the limitation of side-effects such as constipation and
sedation which are typically seen with systemic administration. Given locally into
the tail, morphine and other opioids are effective analgesics, working either alone
peripherally or synergistically at central sites (Kolesnikov *et al.*, 1996). In many
30 respects, these studies are similar to clinical investigations (Stein, 1993; Dahl *et al.*,
1990; Dalsgaard *et al.*, 1994; Heard *et al.*, 1992; Joris *et al.*, 1987; Khoury *et al.*,
1992; Mays *et al.*, 1987; Raja *et al.*, 1992). Peripheral mechanisms also have been
implicated in systemic morphine tolerance (Kolesnikov *et al.*, 1996). Early studies
35 reported that systemic morphine tolerance does not alter the sensitivity to morphine
given either spinally or supraspinally (Roerig *et al.*, 1984). Although we also found

potency to remain unchanged for spinal or supraspinal morphine following chronic morphine dosing, a profound reduction in its potency peripherally was observed (Kolesnikov *et al.*, 1996).

SUMMARY OF THE INVENTION

The present invention relates to method and compositions for providing topically administered N-methyl-D-aspartate (NMDA) receptor antagonists to obtain more efficient peripheral analgesia using an analgesic that functions through an opiate receptor and for tolerance inhibition and/or tolerance reversal to the analgesic.

The present invention provides a topical pharmaceutical composition comprising an N-methyl-D-aspartate receptor antagonist alone or in combination with at least one analgesic that functions through an opiate receptor and a pharmaceutically acceptable topical excipient.

Another aspect of the invention is a method of providing analgesia to a mammal comprising systemic or topical administration of an analgesic that functions through an opiate receptor, and which analgesic is administered before, with, or following the topical administration to the mammal of a tolerance-reducing or tolerance-inhibiting amount of at least one N-methyl-D-aspartate receptor antagonist.

Another aspect of the invention is a method of reversing tolerance in a mammal treated with an analgesic that functions through an opiate receptor comprising the topical administration of an effective tolerance-reversing amount of at least one NMDA receptor antagonist.

The present invention further provides a pharmaceutical tolerance-reducing or tolerance-inhibiting analgesic kit comprising:

- (A) a topical or systemic pharmaceutical composition comprising at least one analgesic that functions through an opiate receptor; and
- (B) a topical pharmaceutical composition comprising at least one tolerance-reducing or tolerance-inhibiting N-methyl-D-aspartate receptor antagonist.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1a and 1b: Topical opioid analgesia in the mouse

1a) Groups of mice received a 2 min topical exposure to morphine (15 mM; n=20), DAMGO (2 mM; n=10) or M6G (20 mM; n=10) and were tested in the tailflick assay.

1b) Dose-response curves were generated for each of the designated compounds applied topically for 1 min, as described in Methods. Each dose of drug had at least 10 mice/group.

Fig. 2a and 2b: Effects of opioid antagonists on topical Mu analgesia

2a) Groups of mice ($n \geq 10$) received either morphine (15 mM), DAMGO (2 mM) or M6G (20 mM) topically for 1 min alone or with naloxone (1 mg/kg, s.c.) injected subcutaneously on the back 20 min prior to the analgesic agonists. Naloxone, a Mu receptor antagonist, significantly reduced the responses for all agonists.

2b) Groups of mice ($n \geq 10$) received either morphine (15 mM), DAMGO (2 mM) or M6G (20 mM) topically for 1 min alone or with 3-methoxynaltrexone (3-MeONTx; 0.25 mg/kg, s.c.) injected subcutaneously on the back 20 min prior to the agonists. 3-MeONTx significantly lowered the response only for M6G.

Fig. 3a and 3b: Interactions between topical and either systemic or spinal morphine

3a) Groups of mice ($n \geq 10$) received topical morphine (15 mM; 2 min) alone, or with spinal (100 ng, i.t.) or systemic (1 mg/kg, s.c.) morphine. The spinal morphine dose alone had no observable action and the systemic dose produced only a 10% response. At 30 min, when the response to topical drug alone was lost, the responses of the combinations were significantly greater.

3b) Left: Groups of mice ($n \geq 10$) received topical morphine (15 mM; 2 min) alone, spinal morphine (100 ng, i.t.) alone or both together. Testing was performed 10 min following drug administration. At this time point, topical morphine alone had a 30% response. The combined dosing was significantly more active than the sum of the two individual routes alone. **Right:** Groups of mice ($n \geq 10$) received topical morphine (15 mM) alone, systemic morphine (1 mg/kg, s.c.) alone or both together. Testing was performed 30 min following drug administration. At this time point, topical morphine alone had no observable response. The combined dosing was significantly greater than the sum of the two ones alone.

Fig. 4: Tolerance to systemic and topical morphine

Groups of mice ($n \geq 10$) received either morphine systemically (5 mg/kg, s.c.) or topically (15 mM; 1 min). DMSO alone had no observable effect on days 1, 2 or 3. On day 3, the response in the systemic group was significantly greater than the topical group.

Fig. 5: Cross tolerance between morphine and DAMGO and M6G

Groups of mice ($n \geq 10$) received morphine (5 mg/kg, s.c.) or saline daily for five days. On the sixth day, the mice were tested after local exposure (1 min) to morphine (15 mM), M6G (20 mM) or DAMGO (2 mM). The response to morphine and DAMGO after chronic morphine treatment was significantly decreased ($p < 0.01$). There was no change in the response to M6G.

Fig. 6a, 6b and 6c: Effects of MK801 on topical morphine tolerance

6a) Groups of mice ($n \geq 10$) received topical morphine (15 mM; 1 min) alone or with MK801 given either topically (3 mM), systemically (0.1 mg/kg, s.c.) or intrathecally (1 μ g, i.t.). After three days the response to morphine alone was lost ($p < 0.01$), as was the response to morphine with intrathecal MK801 ($p <$

0.01). The combination of morphine with either systemic or topical MK801 remained essentially unchanged for five days.

6b) Groups of mice ($n \geq 10$) received topical morphine (15 mM; 1 min) alone, topical MK801 alone (3 mM) or topical morphine (15 mM) with topical MK801 at the indicated concentration (0.15, 0.3 or 3 mM). After three days, the response to morphine alone was lost ($p < 0.01$). The two higher MK801 doses prevented the loss of responsiveness ($p < 0.01$) while the lowest doses gave an intermediate response.

6c) Groups of mice ($n \geq 10$) received topical morphine (15 mM; 1 min) alone for three days. Starting on the fourth day, they received topical morphine with topical MK801 at either 0.3 or 3 mM. Coadministration of topical MK801 with topical morphine reversed the previously established tolerance ($p < 0.01$).

Figure 7a and b: Effect of ketamine on topical morphine tolerance

7a: Groups of mice ($n=20$) were treated topically once daily for 3 days with morphine (15mM) alone (closed circles) or both morphine with ketamine at 3.6mM (triangles) or 36mM (open circles). Ketamine alone (36mM) did not produce significant analgesia in this model. After three days, the response to morphine alone was lost ($p<0.001$). The lower ketamine dose (3.6mM) significantly lessened the loss of morphine analgesic response after three days ($p<0.05$). The higher ketamine dose (36mM) prevented tolerance up to six days ($p<0.0001$).

7b. Groups of mice ($n=20$) received topical morphine (15mM) alone (closed circles) for two days. Starting on the day 3, the two groups of mice received daily doses of morphine in conjunction with either ketamine at either 3.6 (triangles) or 36mM (squares) through day 6. The higher ketamine dose (36mM) completely restored morphine analgesia ($p<0.0001$).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a topical pharmaceutical composition comprising of at least one N-methyl-D-aspartate (NMDA) receptor antagonist alone

-6-

or in combination with at least one analgesic that functions through an opiate receptor and a pharmaceutically acceptable topical excipient.

N-methyl-D-aspartate receptor antagonists for use in the present invention include but are not limited to morphinans such as dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and dextrophan ((+)-3-hydroxy-N-methylmorphinan), MK-801 ((5R, 10S) - (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5,10-immine hydrogen maleate), ketamine (2-(2-chlorophenyl)-2-(methylamino) cyclohexanone), pyroloquinoline quinone and cis-4-(phosphonomethyl)-2-piperidine carboxylic acid, memantine (3,5-dimethyl-9-adamantanamine hydrochloride), their mixtures and the pharmaceutically acceptable salts thereof, and the like. Except for dextromethorphan, many current NMDA receptor antagonists have not been suitable for systemic clinical use due to profound psychomimetic side effects. Such NMDA receptor antagonists, however, may be used in the present invention in topical formulations. Topical use of these NMDA receptor antagonists allows for interference and attenuation of tolerance development to analgesics without producing limiting side effects. NMDA receptor antagonists that may be used in topical formulations include but are not limited to MK 801, dextromethorphan, ketamine, memantine, dextrophan, their mixtures and pharmaceutically acceptable salts thereof, pyroloquinoline quinone, cis-4-(phosphono-methyl)-2-piperidine carboxylic acid, their mixtures and pharmaceutically acceptable salts thereof, and the like.

Analgesics which may be used in the present invention are those that provide analgesia through activation of at least one type of opiate receptor. The opiate receptors that may be activated by the analgesic component of the present invention include but are not limited to any one or combination of delta (δ) opiate receptors, kappa (κ) opiate receptors and Mu opiate receptors. The analgesics include but are not limited to opiates, opiate derivatives, and synthetic opioids, endogenous or synthetic opioid peptides such as enkephalins, endorphins and their pharmaceutically acceptable salts. Specific examples include ethylmorphine, hydromorphone, morphine, codeine, oxymorphone, [D-Ala², MePhe⁴,

Glycol)³]enkephalin (DAMGO), propoxyphene, buprenorphine, oxycodone, hydromorphone, hydromorphone, fentanyl, sufentanil, pentazocine, nalbuphine, nalorphine, heroin, levorphanol, levallorphan, methadone, meperidine, cocaine, dihydrocodeine, hydrocodone, nalmefene, naloxone, naltrexone, butorphanol, and the pharmaceutically acceptable salts and the like.

Optionally, the topical pharmaceutical composition of the present invention may further comprise a local anesthetic including but not limited to lidocaine, bupivacaine, meprivacaine, ropivacaine, tetracaine, benzocaine and the like.

As used herein, a mammal that may benefit from the methods of treatment of the present invention is any warm-blooded animal in need of treatment for pain. Mammals include but are not limited to humans, primates, dogs, cats, rodents, horses, cattle, sheep, and the like. The analgesic is provided to a mammal in need of relief from pain. The pain may be an acute or chronic pain. Diseases or conditions which may necessitate analgesia include but are not limited to pain associated with trauma, amputation, neuropathy, fibromyalgia, burns, abrasions, infections, lacerations, incisions and the like.

This invention provides for attenuating or preventing the development of tolerance associated with the administration of narcotic analgesics. Accordingly, NMDA receptor antagonists may be administered in amounts which are effective for either attenuating or preventing tolerance development. As used herein, the term tolerance preventing, tolerance-inhibiting or tolerance-reversing dose is an amount of an NMDA receptor antagonist effective to maintain and/or restore, or at least partially restore, the analgesic effect of the narcotic analgesic.

In a method of providing peripheral analgesia to a mammal, a tolerance-attenuating or preventing dose of at least one NMDA receptor antagonist is administered topically prior to, concurrently or following topical administration of at least one analgesic that functions through an opiate receptor.

In one embodiment of the method of providing analgesia to a mammal, a tolerance-attenuating or inhibiting dose of the NMDA receptor

antagonist, ketamine is administered topically prior to, concurrently or following topical administration of the opiate analgesic, morphine.

In another embodiment of the method of providing analgesia to a mammal, a tolerance inhibiting or tolerance-reversing dose of the NMDA receptor antagonist, dextromethorphan, is administered topically prior to, concurrently or following topical administration of the opiate analgesic, morphine.

Administration of a topical pharmaceutical composition of the invention may be in the form of a single dosage unit comprising the NMDA receptor antagonist alone or in combination with the analgesic in a topical formulation in effective amounts.

The concentration of the topical NMDA receptor antagonist in the pharmaceutical composition is in a range of about 0.1% to about 5% by weight in mixture but may vary in amounts depending on particular antagonist used and the particular analgesic being administered to the mammal. The concentration of the topical NMDA receptor antagonist provides a dose-lowering effect on the concentration of analgesic needed to provide effective analgesia. For example, a concentration of analgesic, when used in combination with a topical NMDA receptor antagonist may be provided in a range of about 1.0 to about 10% by weight for topical administration of the analgesic, in a range of about 0.1 to about 0.2 mg/kg body weight for systemic administration of the analgesic and in a range of about 1-5 mg for intrathecal administration of the analgesic.

A particular dose of the topical composition may be provided for example, 2-3 times per day, or any period sufficient to prevent, inhibit or reverse tolerance in the mammal receiving an analgesic that functions through an opiate receptor.

The topical pharmaceutical compositions may be formulated as an aqueous solution, lotion, gel, cream ointment, adhesive film and the like, with pharmaceutically acceptable excipients such as aloe vera, propylene glycol, DMSO, lecithine base, and the like. DMSO, as used in the present invention, does not provide systemic adsorption of the therapeutic. A gel excipient may comprise one

or more of the following - petrolatum, lanoline, polyethylene glycols, bee wax, mineral oil, diluents, such as water and alcohol, and emulsifiers and stabilizers.

Aqueous suspensions can contain the composition in admixture with pharmaceutically acceptable excipients such as suspending agents, e.g., sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as naturally occurring phosphatide, e.g., lecithin, or condensation products of an alkylene oxide with fatty acids, e.g., polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, e.g., heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, e.g., polyoxyethylene sorbitol monooleate or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, e.g., polyoxyethylene sorbitan monooleate. Such aqueous suspensions can also contain one or more preservatives, e.g., ethyl or n-propyl-p-hydroxy benzoate.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the composition in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

The composition of this invention or either of its principal active ingredients can be provided in sustained release dosage formulations as are known in the art.

A topical formulation of the present invention delivers a therapeutic effect on the peripheral opiate receptors and is not required to deliver the active ingredients in the topical formulation to central (brain and spinal cord) opiate receptors. The topical formulations of the present invention provides local delivery of the active ingredients and is not required to provide systemic delivery of the active ingredients in the formulation in the treated mammals.

Topical administration of the pharmaceutical composition may be accomplished by application of a solution, gel, lotion, ointment, cream or other vehicle topically used to deliver therapeutics to a local site. One means of application is by spraying the composition over the area to be treated. In another embodiment, a patch which provides a sustained release topical formulation may also be used to administer the topical therapeutic. The patch may be a reservoir and porous membrane type or a solid matrix as are known in the art. The active agents may be in a plurality of microcapsules distributed throughout the permeable adhesive layer.

In another embodiment of the method of providing analgesia to a mammal with pre-existing tolerance to an analgesic, a tolerance-reversing dose of at least one NMDA receptor antagonist is topically administered concurrently or following topical or systemic administration of at least one analgesic that functions through an opiate receptor.

The pharmaceutical composition of the NMDA receptor antagonist for topical administration may also be provided in kit form, along with at least one topical or systemic pharmaceutical composition comprising an analgesic that functions through an opiate receptor.

The present invention also encompasses a method of providing analgesia to a mammal comprising topical administration of at least one analgesic that functions through an opiate receptor prior to, concurrently, or following systemic or intrathecal administration of at least one analgesic. The combination of topical administration with systemic or intrathecal administration of the analgesic provides effective and therapeutic analgesia at low doses of the topical analgesic and low doses of systemic or intrathecal analgesic with concomittant lowering of detrimental side-effects of the analgesic. The doses used in the combination therapy are doses that are lower than the dose required to achieve a therapeutic level of analgesia using either analgesic, alone. The concentration of the topical analgesic in a pharmaceutical composition for use in the combination analgesic therapy is in a range of about 1 to about 10% by weight. The concentration of the systemic

analgesic in a pharmaceutical composition for use in the combination analgesic therapy is in range as so to provide about 0.1 to about 0.2 mg/kg body weight. In the case of intrathecal administration of an analgesic, in combination with a topical analgesic, the concentration of the intrathecal analgesic is in a range of about 1 to about 5 mg. The therapy may be supplemented by administration of a tolerance-attenuating or tolerance-preventing dose of at least one topical NMDA receptor antagonist. The topical NMDA receptor antagonist may be provided in a concentration range of about 0.1% to about 5% by weight of the formulation.

In one embodiment of a method of providing analgesia to a mammal, topical morphine is administered prior to, concurrently or following systemic or intrathecal administration of morphine.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and therefore such adaptations and modifications are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments.

All references and patents referred to are incorporated herein by reference.

Example 1

Materials and Methods

Male Crl:CD-1(ICR)BR mice (25-30 g; Charles River Breeding Laboratories, Bloomington, MA) were maintained on 12 -h light/dark cycle with food and water available ad libitum. Mice were housed in groups of five until testing. [¹²⁵I]Nal (1680 Ci/mmol) was purchased from New England Nuclear (Boston, MA). Morphine, morphine-6 β -glucuronide (M6G) and [D-Ala², MePhe⁴, Gly(ol)⁵]enkephalin(DAMGO) were generously provided by the Research Technologies Branch of National Institute on Drug Abuse (Rockville, MD). MK801 was purchased from Research Biochemicals, Inc. (Natick, MA).

-12-

Systemic drugs were given subcutaneously (s.c.) in the midscapular region of the back. Intracerebroventricularly (i.c.v.) and intrathecal injections were performed under light halothane anesthesia 30 and 15 min before testing, respectively, as previously reported (Kolesnikov *et al.*, 1996). The i.c.v. injections were administered- 2 mm caudal and 2 mm lateral to the bregma at a depth of 3 mm, whereas intrathecal injections were made by lumbar puncture. Drugs were given topically on the tail by immersion of the tail in dimethylsulfoxide (DMSO) solutions containing the indicated drugs. The distal portion of the tail (3 cm) was immersed in DMSO solution for 1 min. Tailflick latencies then were determined on the region of the tail immersed in the drug, unless otherwise stated. To ensure a local effect, testing was also done with a more proximal segment of tail not exposed to the drug solution.

Analgesia was assessed with the tail-flick assay, as previously reported (Kolesnikov *et al.*, 1996). The tail was exposed to a focused beam of light and the latency of exposure determined. Base-line latencies ranged from 2.5 to 3.5 sec. A maximum cutoff latency of 10 sec was used to minimize tissue damage in analgesic animals. Testing was performed 30 min after systemic administration, 15 min after either i.c.v or i.t. injections or immediately after termination of topical administration into the tail. Antinociception, or analgesia, was defined quantally as a tailflick latency for an individual mouse which was at least twice its baseline latency. Group comparisons were performed using the Fisher exact test. ED₅₀ values were determined using the Bliss program, as previously reported (Pick *et al.*, 1993). To ensure a local action, in all studies we examined a region of the tail which was immersed in DMSO as well as a more proximal segment which was not exposed. Tailflick latencies from the unexposed portion of the tail were similar to base line latencies. DMSO itself had no activity in this model. Testing regions of the tail exposed and not exposed to the DMSO revealed no significant antinociceptive effect in either location.

[¹²⁵I]Morphine and [¹²⁵I]DAMGO were synthesized at room temperature using the chloramine T method with equimolar amounts of [¹²⁵I]Nal

-13-

and either morphine or DAMGO. The reaction terminated with sodium metabisulfite after 1 minute and the radiolabeled opioid separated from unreacted $N^{125}I$ by a C18-reverse phase SepPak (Chien *et al.*, 1997). The radiolabeled compounds were not further separated from the non-iodinated precursors.

Example 2

Topical morphine and DAMGO analgesia

Prior studies from our group demonstrated a potent local analgesic activity of morphine administered subcutaneously in the tail (Kolesnikov *et al.*, 1996). Morphine also was a potent analgesic when applied topically. The analgesic response to a morphine solution (7.5 mM) progressively increased over time, going from only 25% after 30 seconds to 50% by one minute and 80% after 2 min (data not shown). The onset of the response was quite rapid. Analgesia was detectable within one minute after removal of the tail from the opioid solution, the shortest time tested (Fig. 1a). However, the duration of the morphine response was relatively brief, typically lasting less than 30 min. Using a fixed exposure time, morphine produced a dose-dependent effect (Fig 1b; Table 1). Similar results were observed with DMSO solutions of the mu opioid peptide DAMGO, which was over 5-fold more potent (Fig1b; Table 1).

Table 1: Analgesic activity of topical opioids in CD-1 mice

Opioids	ED ₅₀ (95%CL)	Relative potency
Morphine	8.3 mM (4-13)	1
M6G	9.3 mM (7-14)	0.9
DAMGO	1.6 mM (1-2.5)	5

Analgesic ED₅₀ values with 95% confidence limits were determined using at least three doses of drug in groups of mice (n=10-20/dose) in the tailflick assay. All drugs were administered topically for 1 min, as described in Methods. The ratio of M6G and DAMGO was determined against morphine.

-14-

In addition to its greater potency, DAMGO also had a longer duration of action, lasting almost an hour (Fig. 1a). Like morphine, peak DAMGO actions were seen immediately after removal from the DMSO solution. These analgesic responses were easily reversed by systemic naloxone (1 mg/kg s.c.), confirming the opioid selectivity of the response (Fig 2a). Furthermore, no analgesic response with these agents was seen in the proximal portions of the tail not exposed to the opioid solutions.

To further confirm the selectivity of the method, we looked at the distribution of radioactivity following immersion into a solution containing either [125 I]morphine or [125 I]DAMGO (Table 2). The region of the tail exposed to the solution had high levels of radioactivity. A more proximal portion of the tail which was not directly exposed to the solution had levels of radioactivity <1% of those in the distal portion of the tail immersed in the solution. Furthermore, no detectable levels of radioactivity were seen in blood, brain or spinal cord.

Table 2: Distribution of [125 I]DAMGO following topical administration

Tissue	Radioactivity(cpm/g)	
	125 I-Morphine	125 I-DAMGO
Blood	69 \pm 18	<50
Brain	55 \pm 26	<50
Spinal cord	71 \pm 12	<50
Tail		
Exposed	38,460 \pm 3,455	45,280 \pm 2,637
Unexposed	234 \pm 51	157 \pm 51

-15-

The distal part of the tail (4-4.5 cm) was immersed in [¹²⁵I]-labeled morphine or DAMGO (100 µCi/ml) in DMSO and exposed for 3 min. Brain, spinal cord, blood samples, as well as segments from the exposed and unexposed portions of the tail were obtained within 5 min of exposure, weighed and counted directly in a Packard 5500 Gamma Spectrometer. The unexposed tail was less than a 1 cm from the exposed region. Radioactivity was expressed in cpm per gram tissue (cpm/g). Results are the means ± s.e.m. of three animals for each radiolabeled drug.

Example 3

Topical morphine-6β-glucuronide analgesia

Morphine-6β-glucuronide (M6G) administered locally by subcutaneous injection in the tail was analgesic, but it had a ceiling effect of 30% with doses of 10 or 30 µg (data not shown). In the topical paradigm, M6G yielded a full analgesic response with a peak effect immediately after removal from the solution (Fig. 1a) and a potency similar to that of morphine (Fig 1b; Table 1). As with morphine, proximal tail segments did not display analgesia and the M6G response was readily reversed by systemic naloxone (Fig. 2a). The duration of M6G action following topical administration was similar to that of DAMGO and longer than those of morphine (Fig. 1a). The M6G-selective antagonist 3-methoxynaltrexone (3MeONtx) (Brown *et al.*, 1997) also significantly lowered the M6G response (Fig 2b). In contrast, the same 3MeONtx dose was inactive against the analgesic actions of morphine or DAMGO (Fig 2b). In addition to supporting the selectivity of 3MeONtx for the M6G receptors, these observations strongly supported the presence of functional peripheral M6G receptors.

Example 4**Peripheral/central synergy**

Prior work from our laboratory has suggested a potent synergy between peripheral and central morphine systems. We also examined these interactions following topical administration. Topically, the actions of morphine rapidly dissipated, falling from 80% at 1 min to only 30% at 10 min. No analgesia was seen by 30 min. Minimally active doses of intrathecal or subcutaneous morphine markedly potentiated the response of topical morphine (Fig. 3). This is most dramatic at time points beyond 30 min, at which point the topical response alone was completely lost. At these longer time points, the analgesic responses of the combinations were significantly greater than their additive effects (Fig. 3b).

We next looked at the effects of a fixed dose of topical morphine on the ED₅₀ values of spinal and systemic morphine (Table 3).

Table 3: Effects of topical morphine on systemic and spinal morphine analgesia

Morphine Route	ED ₅₀ value	Topical Shift
Systemic alone	4.3 mg/kg (2.9 - 6.4)	
Systemic + topical	0.66 mg/kg (0.4 - 1.0)	6.5
Spinal alone	550 ng (386 - 822)	
Spinal + topical	46 ng (21 - 84)	12

ED₅₀ values and 95% confidence limits were determined for morphine given systemically alone or in conjunction with a fixed dose of topical morphine (15 mM). Testing was done 30 min following the treatments, at which point there were no observable effects from the topical morphine alone. ED₅₀ values and 95% confidence limits were determined for morphine given intrathecally alone and with a fixed dose of topical morphine (15 mM). Testing was done 15 min

-17-

following the treatments, at which point the topical morphine had only a limited (15%) response.

Topical morphine potentiated the analgesic potency of systemic morphine almost 7-fold, even though it had no activity alone at the time point examined (30 min). Topical morphine also enhanced the potency of intrathecal morphine almost 12-fold. Thus, these results support the earlier suggestions of potentiation between peripheral and central morphine analgesic systems.

Example 5

Peripheral morphine tolerance

Peripheral systems are important in the production of tolerance following systemic administration of morphine (Kolesnikov *et al.*, 1996). The tail immersion approach permits repeated local administration of drug without tissue damage, facilitating the study of peripheral morphine tolerance. Daily topical morphine (15 mM) produced profound tolerance by the third day (Fig. 4), shifting morphine's ED₅₀ value over 9-fold (Table 4). Topical tolerance developed more rapidly and to a greater extent than that seen with daily systemic drug, where 5 days of treatment only shifted the morphine dose-response approximately 2-fold.

Table 4: Tolerance to systemic and topical morphine

Morphine Treatment	ED ₅₀ (95% confidence limits)		Ratio
	Naïve	Tolerant	
Systemic	4.3 mg/kg (2.4-5.9)	8.7 mg/kg (5.4, 9.7)	2
Topical	8.3 mM (4.1-10.2)	78 mM (49, 123)	9.4

Morphine ED₅₀ values following either topical or systemic administration were determined in naïve mice and in groups of mice which had

-18-

received morphine chronically. ED₅₀ values and 95% confidence limits were determined using at least three doses of drug (n = 10-20/dose). In the systemic group, mice received morphine (5 mg/kg, s.c.) daily for four days prior to testing while the topical group were treated with a morphine solution (15 mM) daily for two days and the ED₅₀ value determined on the third day. At least three doses of morphine were used to calculate the ED₅₀ values.

Mice given morphine systemically showed significant tolerance to topical morphine as well as to the mu peptide DAMGO (Fig. 5). However, the analgesic activity of topical M6G in these mice remained unchanged, confirming the lack of cross tolerance reported previously (Rossi *et al.*, 1996).

Example 6

Blockade of peripheral morphine tolerance by the NMDA antagonists, MK 801

NMDA/nitric oxide cascade plays an important role in the production of morphine tolerance (Kolesnikov *et al.*, 1993). Blockade of this system prevents the development of morphine tolerance without interfering with analgesia. The NMDA antagonist MK801 given systemically also prevented the development of tolerance to topical morphine (Fig. 6a). Topical MK801 also blocked morphine tolerance as effectively as systemic drug (Fig. 6a), but intrathecal MK801 was ineffective. Topical MK801 actions were dose-dependent, with 0.3 mM effectively blocking tolerance (Fig. 6b).

Furthermore, topical MK801 could reverse pre-established tolerance (Fig. 6c). After treating mice with topical morphine alone for three days the analgesic response was eliminated. Adding MK801 to the treatment regimen restored analgesic sensitivity over the next two days despite the continued administration of morphine. The higher MK801 dose was slightly more effective than the lower one. The slow rate reversal with no effect after the first dose argued strongly against a simple potentiation of morphine potency.

Example 7

Blockade of Peripheral Morphine Tolerance

by the NMDA Antagonist, Ketamine

Daily topical morphine (15mM) led to tolerance with the complete loss analgesia by the third day (Fig 7A and B). The NMDA receptor antagonist ketamine given systemically prevented the development of tolerance to topical morphine, but intrathecal ketamine was ineffective (data not shown). Topical ketamine co-administered with morphine blocked tolerance as effectively as systemic drug in a dose-dependent manner (Fig. 7A). The lower dose (3.6mM) delayed the appearance of tolerance, but the higher dose (36mM) effectively blocked tolerance. Ketamine alone had no appreciable effect in this assay.

Topical ketamine also reversed pre-established tolerance (Fig. 7B). After treating mice with a fixed concentration of topical morphine alone for three days the mice displayed no analgesia. Ketamine added to the treatment regime restored analgesic sensitivity over next three days despite the continued administration of morphine.

The ability of topical ketamine to prevent and/or reverse morphine tolerance implies a peripheral mechanism of action and is similar to the above experiment with dizocilpine (MK-801). Mechanistically, these observations are consistent with the possibility that peripheral tolerance is mediated through peripheral NMDA receptors, possibly on the same dorsal root ganglia neurons containing the opioid receptors.

Discussion

Peripheral opioid actions are becoming increasingly important in our understanding of opioid actions, as demonstrated by the role of peripheral and central synergy in the actions of systemic morphine (Kolesnikov *et al.*, 1996). Furthermore, peripheral sites of action play a major role in the development of tolerance to systemic drug. Exploring peripheral mechanisms is not simple. Earlier studies utilized local injections into the tail to examine peripheral mechanisms. Although useful, this approach has a number of disadvantages, particularly when looking at repeated dosing. In an effort to avoid this problem, we have developed a

-20-

topical approach which is generally applicable to both alkaloids and peptides. The tail immersion technique has a number of advantages. Foremost is the ability to repeatedly treat the mice without tissue damage secondary to injections. The paradigm was selective for local mechanisms. Testing proximal regions of the tail failed to reveal any analgesic response, confirming the distribution studies with ^{125}I -opioid which documented the localization of the radiolabel only to the regions immersed in the drug solution and the absence of any detectable uptake into the blood or central nervous system. Equally important, DMSO alone had no effects in the tailflick assays. Presumably, the activity of this approach is not limited to DMSO and other solvents or topical creams could be used. We had not anticipated that topical solutions of peptides would be active, but a number of different mu and delta peptides are effective in this paradigm. Clearly, topical approaches open new possibilities clinically for these peptides which are not very effective systemically. Thus, the topical approach provides a useful approach for the examination of peripheral opioid mechanisms and as a therapeutic in pain management.

Peripherally, all the opioids tested were effective analgesics. Of the three, DAMGO was the most active. The similar potencies of morphine and M6G peripherally contrasts with their central actions, where M6G is approximately 100-fold more active than morphine. In all cases, the proximal segments of the tail which were not exposed to the opioid solution were not analgesic, confirming the peripheral site of action for the sites immersed in the opioid solution. The responses were readily antagonized by naloxone. Centrally, 3-MeONTx selectively reverses M6G analgesia without interfering with morphine analgesia, consistent with a different receptor mechanism of action (Brown *et al.*, 1997). 3-MeONTx also reversed peripheral M6G analgesia without affecting either DAMGO or morphine actions. Thus, peripheral M6G analgesia showed the same antagonist selectivity as seen centrally.

Prior studies had documented synergy between peripheral and central morphine actions. The current studies confirmed these earlier observations. Combining topical morphine with morphine given either systemically or spinally

revealed marked potentiation of the responses beyond those expected for simple additive interactions. Thus, if topical opioids were to be used clinically, these results would suggest that they would be most effective in combination with systemic dosing. By lowering the necessary doses of systemic drug, topical opioids might greatly diminish the side-effects currently associated with opioid analgesics.

Chronic dosing with systemic morphine treatment leads to tolerance.

Localizing the site of morphine tolerance has been difficult. Mice tolerant to systemic morphine show normal sensitivities to morphine given either spinally or supraspinally (Roerig *et al.*, 1984), but not peripherally (Kolesnikov *et al.*, 1996). Indeed, the 19-fold shift in the local morphine dose-response curves far exceed the shift following systemic administration. Our current studies support a role for peripheral sites in morphine tolerance. Chronic topical morphine produced tolerance very rapidly, decreasing the response to undetectable levels by three days corresponding to over a 9-fold shift in the dose-response curve. Chronic dosing with DMSO alone had no effect. The rate of development of tolerance to equianalgesic doses of systemic drug was slower and to a smaller extent, shifting the dose-response curve only 2-fold after 5 days. Mice tolerant to peripheral morphine were cross tolerant to DAMGO, but not to M6G. This lack of cross tolerance is consistent with the selective reversal of M6G analgesia by 3-MeONTx and is consistent with a unique receptor mechanism of M6G action.

N-Methyl-D-aspartate (NMDA) receptor antagonists or nitric oxide synthase (NOS) inhibitors prevent the production of morphine tolerance (Trujillo and Akil, 1994; Gutstein and Trujillo, 1993; Ben-Eliyahu *et al.*, 1992; Kolesnikov *et al.*, 1993). In view of the importance of peripheral opioid mechanisms in tolerance in these paradigms, we looked at the role of peripheral NMDA antagonists. Topical morphine tolerance was effectively blocked by MK801 given systemically or topically, but not spinally. Systemic MK801 would be expected to have access throughout the animal, including peripheral sites, while the intrathecal drug would be restricted to central sites. Likewise, topical ketamine prevented and/or reversed morphine tolerance. Thus, only treatments with access to peripheral sites were

active in this model, implying that peripheral NMDA receptors are responsible for mediating topical morphine tolerance. Recent evidence supports the presence of excitatory amino acid (EAA) receptors on peripheral cutaneous axons (Carlton *et al.*, 1995; Davidson *et al.*, 1997; Zhou *et al.*, 1996). Additional studies are needed to verify the site of action. However, the activity of topical NMDA antagonists opens many clinical possibilities in pain management. Many of the current NMDA receptor antagonists are not suitable for clinical use due to profound psychomimetic side-effects. Restricting their use to topical formulations may provide a way of utilizing their ability to interfere with tolerance development without producing limiting side-effects.

Peripheral opioids clearly have important roles in analgesia and tolerance. The ability of topical opioids to produce analgesia alone and potentiate systemic drugs offers a new approach which may prove useful clinically. The activity of topical peptides further enhances this approach since it opens the way for many highly selective agents acting through non-mu opioid receptor mechanisms. Finally, the ability to block topical tolerance with peripherally acting NMDA antagonists is another exciting advance in the clinical treatment of pain.

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WE CLAIM:

1. A topical pharmaceutical composition comprising at least one
N-methyl-D-aspartate (NMDA) receptor antagonist and at least one analgesic that
functions through an opiate receptor and a pharmaceutically acceptable topical
excipient.

2. The topical pharmaceutical composition according to claim 1
comprising at least one analgesic and wherein the analgesic is selected from the
group consisting of an opiate, an opiate derivative, an opioid, enkephalins,
endorphins and synthetic opioid peptides.

3. The topical pharmaceutical composition according to claim 2,
wherein the opioid is selected from the group consisting of ethylmorphine,
hydromorphone, morphine, oxymorphone, codeine, levorphanol, oxycodone,
pentazocine, propoxyphene, fentanyl, sufentanil, lofentanil, morphine-6-glucuronide
and buprenorphine.

4. The topical pharmaceutical composition according to claim 2,
wherein the enkephalin is selected from the group consisting of [D-Ala², MePhe⁴,
Gly (ol)⁵] enkephalin, and endomorphines.

5. The topical pharmaceutical composition according to claim 1,
wherein the analgesic is morphine.

6. The topical pharmaceutical composition according to claim 1,
wherein the NMDA receptor antagonist is selected from the group consisting of
dextromethorphan, dextrorphan, ketamine, pyroloquinoline quinone, cis-4-
(phosphonomethyl)-2-piperidine carboxylic acid, MK801, memantine, and their
mixtures and pharmaceutically acceptable salts thereof.

7. The topical pharmaceutical composition according to claim 1
further comprising a local anesthetic.

8. The topical pharmaceutical composition according to claim 7, wherein the local anesthetic is selected from the group consisting of lidocaine, bupivacaine, mepivacaine, ropivacaine, tetracaine and benzocaine.

9. A method of providing peripheral analgesia to a mammal comprising topical administration of a tolerance-attenuating or preventing dose of at least one NMDA receptor antagonist prior to, concurrently, or following topical administration of at least one analgesic that functions through an opiate receptor.

10. The method according to claim 9, wherein the NMDA receptor antagonist is selected from the group consisting of dextromethorphan, dextrorphan, ketamine, pyroloquinoline quinone, cis-4-(phosphonomethyl)-2-piperidine carboxylic acid, MK801, memantine, and their mixtures and pharmaceutically acceptable salts thereof.

11. The method according to claim 9, wherein the analgesic is selected from the group consisting of an opiate, an opiate derivative, an opioid, enkephalins and endorphins.

12. The method according to claim 11, wherein the opioid is selected from the group consisting of ethylmorphine, hydromorphone, morphine, oxymorphone, codeine, levorphanol, oxycodone, pentazocine, propoxyphene, fentanyl, sufentanil, lofentanil, morphine-6-glucuronide and buprenorphine.

13. The method according to claim 9, wherein the enkephalin is selected from the group consisting of [D-Ala², MePhe⁴, Gly (ol)⁵] enkephalin, and endorphines.

14. The method according to claim 9, wherein the NMDA receptor antagonist is administered in a dose of about 0.1% to about 5%.

15. A method of providing analgesia to a mammal with pre-existing tolerance to an analgesic comprising topical administration of an effective

-28-

tolerance-reversing dose of at least one NMDA receptor antagonist concurrently or following topical or systemic administration of at least one analgesic that functions through an opiate receptor.

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16. A pharmaceutical tolerance-inhibiting analgesic kit comprising:

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(a) a topical or systemic pharmaceutical composition comprising at least one analgesic that functions through an opiate receptor; and

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(b) a topical pharmaceutical composition comprising at least one tolerance-inhibiting NMDA receptor antagonist.

17. A method of providing analgesia to a mammal comprising topical administration of at least one analgesic that functions through an opiate receptor prior to, concurrently or following systemic or intrathecal administration of a second analgesic that functions through an opiate receptor.

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18. The method according to claim 17, further comprising topical administration of a tolerance-attenuating or preventing dose of at least one NMDA receptor antagonist.

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Fig. 1a

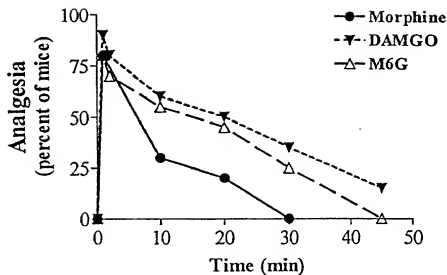


Fig. 1b

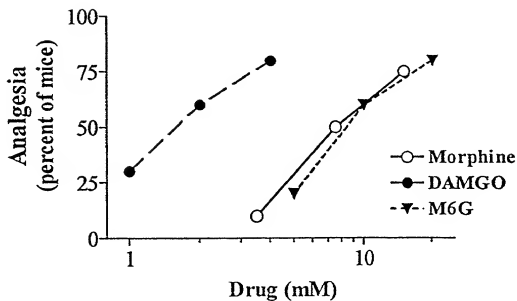


Fig. 2a

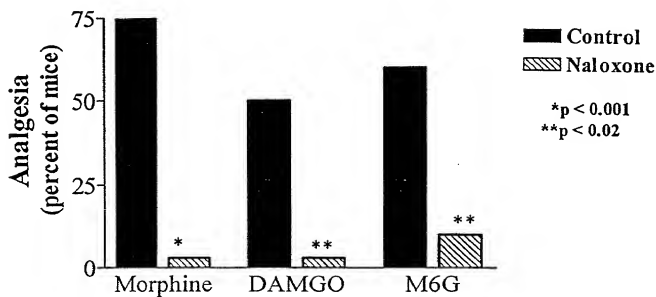


Fig. 2b

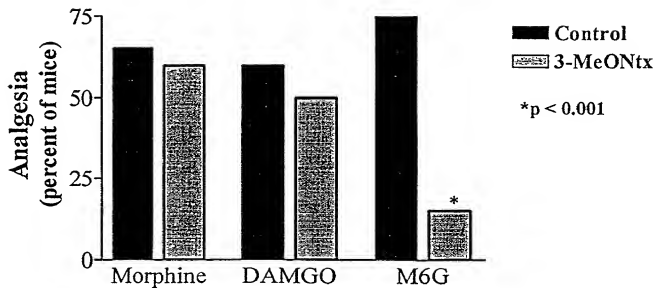


Fig. 3a

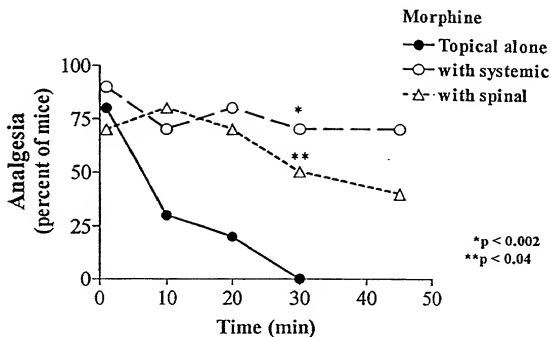


Fig. 3b

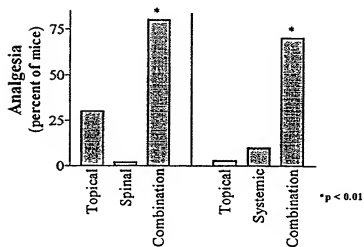


Fig. 4

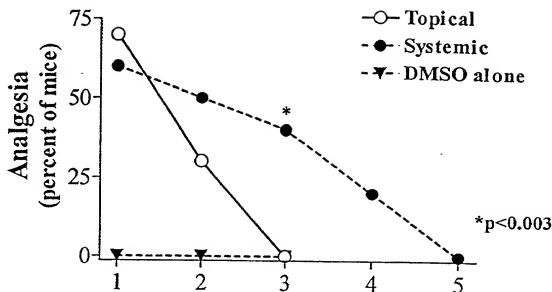
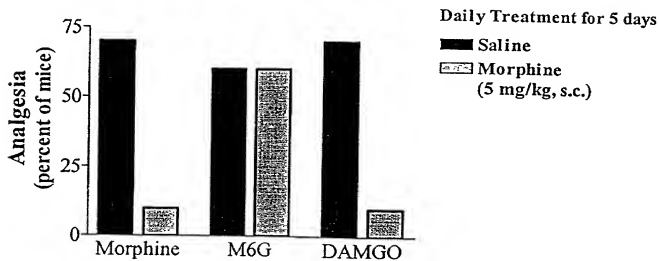


Fig. 5



5/6

Fig. 6a

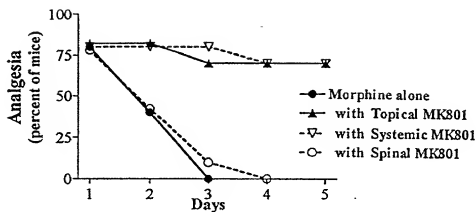


Fig. 6b

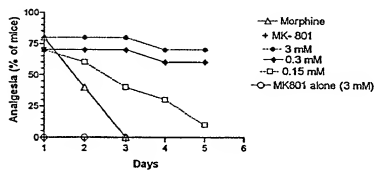
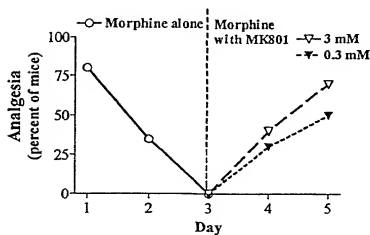
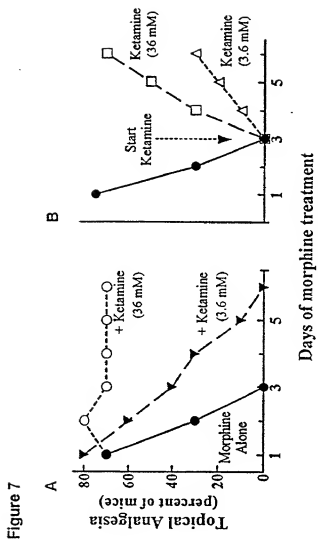


Fig. 6c



6/6



DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes reference to PCT International Applications)

FROMMER LAWRENCE & HAUG, LLP
File No.: 830010-2006.2

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and joint inventor (if plural, names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention ENTITLED:

**TOPICAL COMPOSITIONS COMPRISING AN OPIOID ANALGESIC
AND AN NMDA ANTAGONIST**

the specification of which:

- ☒ is attached hereto
- ☒ was filed on April 2, 2001, bearing
United States Application Serial No. 09/806,645
- ☒ as the National Phase of PCT Application No. PCT/US99/16049, filed July 15, 1999 and designating the U.S., and published as WO 00/03716 on January 27, 2000,
- ☐ with amendments through DATE EVEN HEREWITH (if applicable, give details).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119 (a) - (d) or § 365 (b) of any foreign application(s) for patent or inventor's certificate, or § 365 (a) of any PCT International application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT International applications designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) on which priority is claimed:

Prior Foreign/PCT Application(s) [list additional applications on separate page]:

<u>Country (or PCT)</u>	<u>Application Number:</u>	<u>Filed (Day/Month/Year)</u>	<u>Priority Claimed:</u>	
			<u>Yes</u>	<u>No</u>

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

<u>60/092,082</u>	<u>July 16, 1998</u>
(Application Number)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code § 120 of any United States application(s) or § 365 (c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior United States or PCT International application(s) in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Prior U.S. (or U.S.-designating PCT) Application(s) [list additional applications on separate page]:

U.S. Serial No.: Filed (Day/Month/Year) PCT Application No. Status (patented, pending, abandoned)

PCT	15/JULY/1999	PCT/US99/016049
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I hereby appoint Susan K. Lehnhardt, Reg. No. 33,943 and FROMMER LAWRENCE & HAUG, LLP or their duly appointed associates, my attorneys or agents, with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to file continuation and divisional applications thereof, to receive the Patent, and to transact all business in the Patent and Trademark Office and in the Courts in connection therewith, and to insert the Serial Number of the application in the space provided above, and specify that all communications about the application are to be directed to the following correspondence address:

Susan K. Lehnhardt, Esq.
c/o FROMMER LAWRENCE &
HAUG LLP
745 Fifth Avenue
New York, NY 10151
FAX (212) 588-0500

Direct all telephone calls to: (212) 588-0800
to the attention of:
Susan K. Lehnhardt, Esq.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

INVENTOR(S):

Signature:  Date: 6/20/01

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Signature:  Date: 6/20/01

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Citizenship: United States of America.

Post Office Address(es) of inventors [if different from residence]:

NOTE: In order to qualify for reduced fees available to Small Entities, each inventor and any other individual or entity having rights to the invention must also sign an appropriate separate "Verified Statement (Declaration) Claiming [or Supporting a Claim by Another for] Small Entity Status" form [e.g. for Independent Inventor, Small Business Concern, Nonprofit Organization, Individual Non-Inventor].